Okosieme, O., Taylor, P., Evans, C., Thayer, D., Chai, A., Khan, I., Draman, M., Tennant, B., Green, J., Sayers, A., French, R., Lazarus, J., Premawardhana, L., & Dayan, C. (2019). Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. *Lancet Diabetes and Endocrinology*, *7*(4), 278-287. https://doi.org/10.1016/S2213-8587(19)30059-2

Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study

Supplementary Appendix

Supplementary Methods

Modified Charlson Comorbidity Scores

Comorbidity scores were derived using a modification of the Charlson Comorbidity Index (CCI) [1]. Individual scores were calculated as the sum of weighted scores for each of 17 disease conditions identified from hospital admission data using ICD-10 codes for secondary diagnosis fields (DIAG2-DIAG14) [2,3] (supplementary table 1).

Laboratory assays

Between January 1998 and April 2004 TSH receptor antibodies (TRAbs) were measured with a 2nd generation radioimmunoassay (RIA) based on inhibition of labelled TSH binding to TSH receptor coated tubes, RSR Limited, Cardiff [4,5]. The assay reference ranges were: <1.0, negative, 1.0-1.5 borderline >1.5, positive with analytical range of 1—40 U/L, and lower detection limit of 0.33 U/L. The sensitivity of the assay was 92.0% with specificity of 100%. Between April 2004 and December 2013, TRAbs were measured with a 2nd generation RIA which was also based on inhibition of radio-labelled TSH binding to TSH receptor coated tubes, B.R.A.H.M.S. TRAK human, Thermo Scientific [6]. The assay reference ranges were: <1.0, negative, 1.0-1.5 borderline, and >1.5, positive, with analytical range of 1—40 U/L, functional sensitivity of 1.0 +/- 0.2 U/L and analytical sensitivity of 0.3 U/L. The sensitivity of the assay was 98.8% with specificity of 99.6%. The assay principles, performance, and reference ranges for thyroid function tests (FT4 and TSH) are presented in supplementary table 2. To account for differences in assay methods, FT4 was transformed to multiples of the upper limit of the assay reference range (ULN) and TSH was categorised as low, normal or high-TSH according to the assay reference range.

Restricted Cubic Spline Regression

We modelled a potential non-linear relationship between the FT4 concentration at one year and mortality or MACE using restricted cubic spline regressions. Cubic splines allow flexible smooth transformations of the relationship between a quantitative covariate and an outcome [7]. We used the *mkspline* co-mmand in Stata to set 4 equally-

spaced knots at percentiles 5, 35, 65 and 95 according to the recommendation by Harrell [8]. Varying the positions of the knots did not significantly influence our estimates. The reference values were set at the FT4 assay upper limit (x 1.0). Predicted hazard ratios (HR) were derived from Cox regression models adjusted for age, gender, year of diagnosis, baseline TRAb concentration, and comorbidity. We used the *xblc* post-estimation package in Stata to plot the regression between FT4 and log HR for mortality/MACE. Models were fitted for the whole cohort and then stratified by treatment. P values for non-linearity were obtained using likelihood ratio tests. We also used cubic splines to model longitudinal change in FT4 concentration in the first year of treatment with cubic knots set at 0, 3, 6, 9, and 12 months.

Missing data imputation

Serial thyroid function tests were available for patients with Graves' disease but not for the control population. Thyroid function tests were missing in 29% of patients. One-year TSH was available in 80% of patients with serial thyroid function tests equivalent to 57% of the eligible landmark cohort. All other variables had complete data. Missing thyroid tests were due to lack of electronic access and linkage of laboratory data to the SAIL databank from some laboratories at various study time segments. Where laboratory linkage occurred, thyroid tests were available in >90% of patients in clinics served by the laboratory, reducing the likelihood of confounding by data not missing at random.

The characteristics of patients with missing and non-missing thyroid tests is shown in supplementary table 3. Patients with missing tests were older (49 vs 47 years) and missing tests were more frequent in patients treated with antithyroid drugs compared to radioiodine or surgery (37% vs 3% vs 16%, P<0.001). Patients with missing tests also had lower TRAb levels (median 5.8 vs 7.8 IU/L) but in logistic regression, the only factors associated with thyroid test missingness were older age (OR 1.01, 95%CI 1.00, 1.02 per year increase in age) and treatment with antithyroid drugs (OR 2.28, 95%CI 1.61, 3.23, antithyroid drugs vs radioiodine/Surgery). Missingness was not associated with sex, comorbidity, TRAB concentration, mortality or MACE. Thus, we assumed the data were not 'Missing Completely at Random, (MCAR)' but were 'Missing at Random, (MAR)'.

In the one-year TSH analysis we addressed missing tests using multiple variable imputation by chained equations [9]. The imputation model comprised all predictor and outcome variables in the analysis. We generated 50 imputed datasets and fitted Cox proportional models within each dataset after which estimates were pooled according to Rubin's rules [10]. In sensitivity analysis we repeated the analysis using a complete case analysis which showed identical estimates to the imputation model (Supplementary figure 1). To exclude the possibility that missingness at one-year was associated with stable or worse disease control, we modelled two sensitivity scenarios in which a normal-TSH and a low-TSH at one-year were assumed for patients with serial TSH but missing one-year TSH. These scenarios gave similar results to the imputation model (data not shown).

References

1. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases* 1987; **40**(5): 373-83.

2. http://www.drfosterhealth.co.uk/hospital-guide/methodology/. 2018.

3. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004; **57**(12): 1288-94.

4. Sanders J, Evans M, Betterle C, et al. A human monoclonal autoantibody to the thyrotropin receptor with thyroid-stimulating blocking activity. *Thyroid* 2008; **18**(7): 735-46.

5. Smith BR, Bolton J, Young S, et al. A new assay for thyrotropin receptor autoantibodies. *Thyroid* 2004; **14**(10): 830-5.

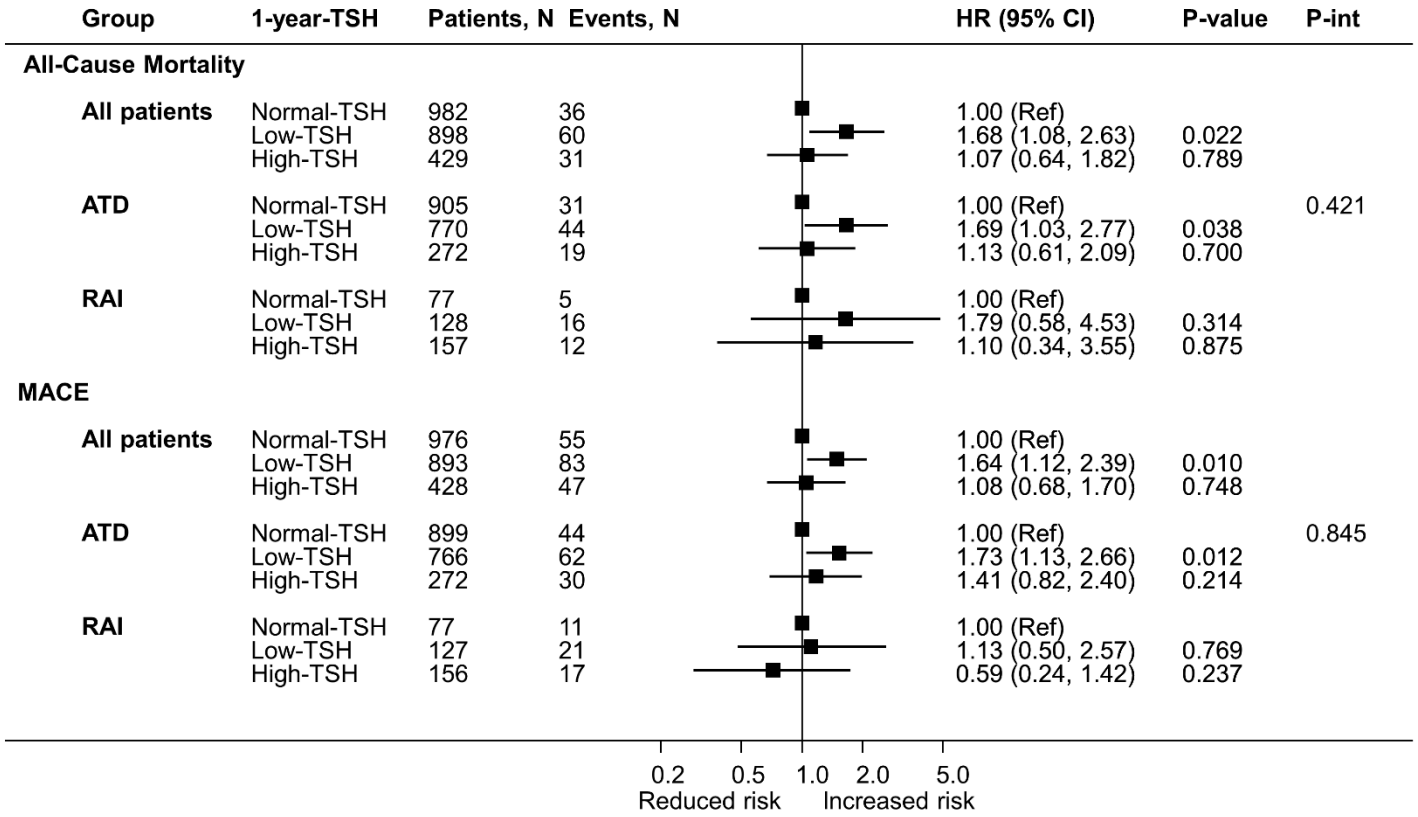
6. Costagliola S, Morgenthaler NG, Hoermann R, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. *J Clin Endocrinol Metab* 1999; **84**(1): 90-7.

7. Orsini N, Greenland S. A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. *Stata Journal* 2011; **11**(1): 1-29.

8. Harrell FE, Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst* 1988; **80**(15): 1198-202.

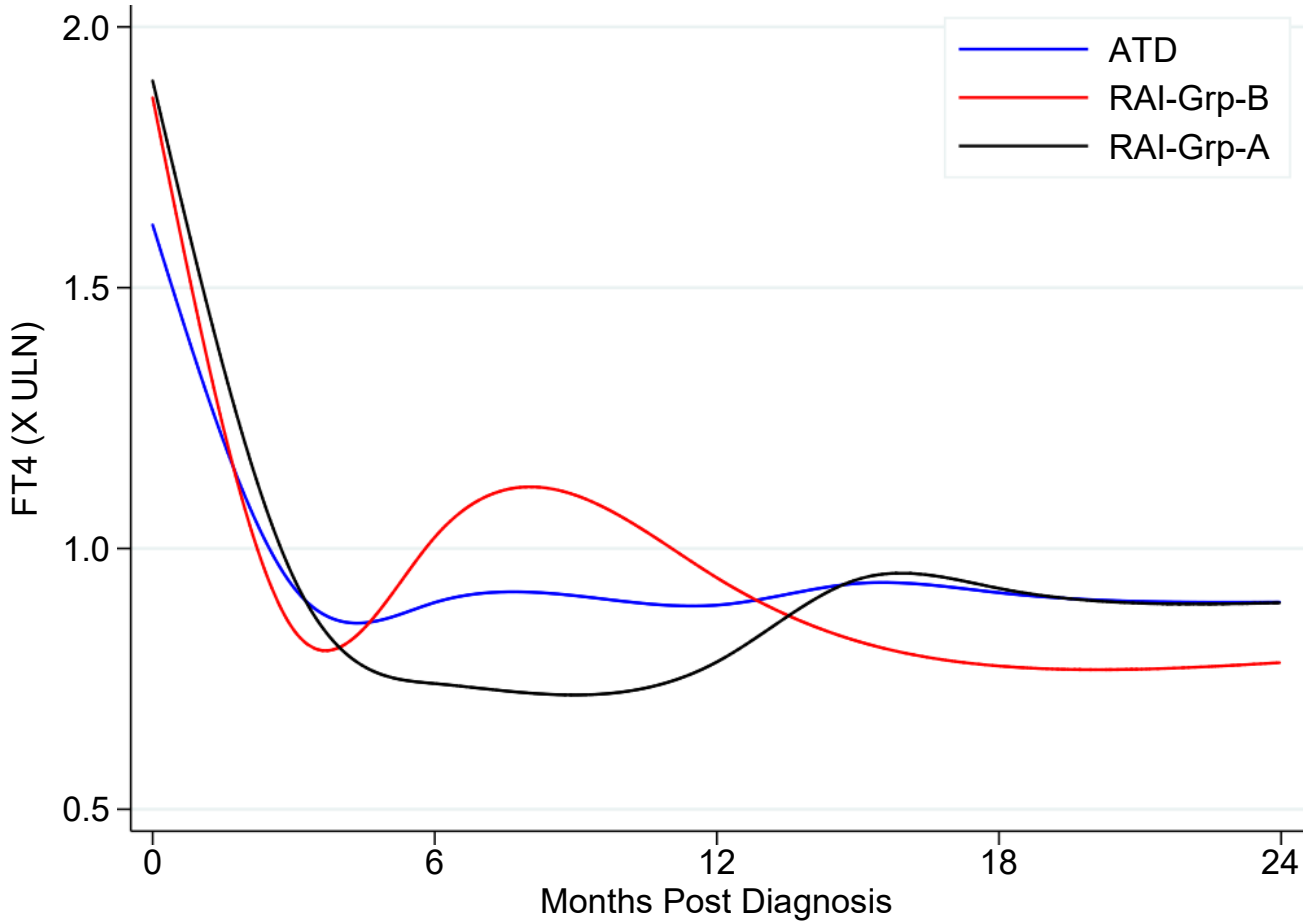
9. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011; **30**(4): 377-99.

10. Rubin D, B. Multiple Imputation for Nonresponse in Surveys. Hoboken, New Jersey, USA: John Wiley and Sons; 2004.



SUPPLEMENTARY FIGURE 1: Hazard ratios for mortality or MACE by one-year TSH, complete case analysis

HR (95% CI) are obtained from multivariable Cox proportional hazard regression models. Analysis was conducted in all patients and in treatment subgroups according to treatment in the first-year with antithyroid drugs (ATD) or radioactive iodine (RAI). P-int, P values for interaction with treatment group. Results are obtained from a complete case analysis



SUPPLEMENTARY FIGURE 2: FT4 profile post-diagnosis

Longitudinal profile of FT4 concentrations after diagnosis according to treatment groups. FT4 is in multiples of the upper limit of the reference range (X ULN); ATD, antithyroid drugs, RAI-Grp-A, radioiodine with control of hyperthyroidism by 12 months, RAI-Grp-B, radioiodine without control of hyperthyroidism by 12 months

		FT4, pmol/L		TSH, mU/L	
Laboratory	**Assay method, platform**	**Reference Interval**	**CV (%)**	**Reference Interval**	**CV (%)**
Cardiff and Vale					
Jan 1998 - May 2011	CCIA, ADVIA Centaur, Bayer[1]	9·8–23·1	2·31 at 13·9 pmol/L	0·35 - 5·50	2·44 at 5·65 mU/L
May 2011 - Jan 2013	CMIA, Abbott ARCHITECT[2]	9·0 –19·1*	<10 at all levels	0·30 - 4·40	<10 at all levels
Cwm Taf (1)					
Jan 1998 - March 2007	CCIA, IMMULITE 2000, DPC[3]	10·3–24·5	<10 at all levels	0·4 - 4·0	<5·0 at all levels
March 2007 - Dec 2013	ECLIA, Roche E-170[4]	10·3–24·5	8·2 at 8·2 pmol/L	0·4 - 4·0	2·4 at 6·67 mU/L
Cwm Taf (2)					
Jan 1995 – April 2011	CCIA, ADVIA Centaur, Bayer[1]	10·0-25·0	<10 at all levels	0·35-5·50**	<10 at all levels
April 2011-Sept 2012	CCIA, ADVIA Centaur, Bayer[1]	10·0-25·0	<10 at all levels	0·35-5·50	<10 at all levels
Sept 2012-Dec 2013	ECLIA, Roche E-170[4]	10·3–24·5	8·2 at 8·2 pmol/L	0·4 - 4·0	2·4 at 6·67 mU/L
Aneurin Bevan (1)					
1998-2006	CCIA, IMMULITE 2000, DPC[3]	11·5–22·7	<10 at all levels	0·4 - 4·0	<5 at all levels
2006-2013	CMIA, Abbott ARCHITECT[2]	9·0–19·1	4·8% at 23·3 pmol/L	0·30 - 4·40	4·1% at 26·8 mU/L
Aneurin Bevan (2)					
1998—2000	MEIA, Abbott Axsym[2]	9·0–19·1	4·6 at 15·4 pmol/L	0·30 - 4·40	4·9 at 2·8 mU/L
2000—2006	CCIA, ADVIA Centaur, Bayer[1]	9·8–23·1	<10 at all levels	0·35 - 5·50	<10 at all levels
2007—2013	CMIA, Abbott ARCHITECT[2]	9·0–19·1	<10 at all levels	0·30 - 4·40	<10 at all levels

Supplementary Table 1: Thyroid hormone assays

CV, coefficient of variation; CCIA, competitive chemiluminescent immunoassay, CMIA, chemiluminescent microparticle immunoassay; ECLIA, electrochemiluminescence immunoassay; MEIA, Microparticle Enzyme Immunoassay; 1. Bayer Diagnostics, Newbury, UK; 2. Abbott Diagnostics, Maidenhead, Berks, UK; 3. Diagnostics Product Corporation, Llanberis, Wales; 4. Roche Diagnostics GmbH, Mannheim, Germany, *from January to December 2013 the reference range for this assay was changed to 9.2—21.0 pmol/L, **from September 2009 to April 2011, reference range for this assay was 0.3-6.0 mU/L

Condition	ICD-10 diagnosis codes	Score
Acute myocardial infarction	I21, I22, I252	1
Congestive heart failure	I50	1
Peripheral vascular disease	I71, I790, I739, R02, Z958, Z959	1
Cerebral vascular disease	I60, I61, I62, I63, I65, I66, G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677, I678, I679, I681, I682, I688, I69	1
Dementia	F00, F01, F02, F051	1
Pulmonary disease	J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65	1
Connective tissue disease	M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353	1
Peptic ulcer disease	K25, K26, K27, K28	1
Liver disease	K702, K703, K73, K717, K740, K742, K746, K743, K744, K745	1
Diabetes	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145	1
Diabetes with complications	E102, E112, E132, E142, E103, E113, E133, E143, E104, E114, E134, E144	2
Hemiplegia or paraplegia	G81, G041, G820, G821, G822	2
Renal disease	N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25	2
Cancer	C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C945, C947, C95, C96	2
Metastatic cancer	C77, C78, C79, C80	3
Severe liver disease	K729, K766, K767, K721	3
HIV	B20, B21, B22, B23, B24	6

Supplementary Table 2: Modified Charlson Comorbidity Scores

Reference [2,3]

	Patients with available thyroid tests					Patients with missing thyroid tests	
	All patients	Medical therapy	Iodine-131	Thyroidectomy	P for trend, treatment groups [a]	All patients	P value, missing vs non-missing [b]
	n=2969	n=1950	n=796	n=223		n=1220	
Age, yrs							
Mean ± SD	47 ± 16	46 ± 16	50 ± 16	39 ± 13	<0·001	49 ± 16	<0.001
<20	42 (1·4)	29 (1·5)	6 (0·8)	7 (3·1)	<0·001	9 (0.7)	
20-29	409 (13·8)	278 (14·3)	81 (10·2)	50 (22·4)		135 (11.1)	
30-39	630 (21·2)	424 (21·7)	133 (16·7)	73 (32·7)		225 (18.4)	
40-49	669 (22·5)	426 (21·9)	191 (24·0)	52 (23·3)		253 (20.7)	
50-59	550 (18·5)	360 (18·5)	170 (21·4)	20 (9·0)		260 (21.3)	
60-69	390 (13·1)	252 (12·9)	120 (15·1)	18 (8·1)		195 (16.0)	
≥70	279 (9·4)	181 (9·3)	95 (11·9)	3 (1·4)		143 (11.7)	
Sex							
Female	2422 (81·6)	1596 (81·9)	633 (79·5)	193 (86·5)	0·050	992 (81.3)	0.841
Male	547 (18·4)	354 (18·2)	163 (20·5)	30 (13·5)		228 (18.7)	
Comorbidity							
Absent	2564 (86·4)	1678 (86·1)	688 (86·4)	198 (88·8)	0·532	1035 (84.9)	0.198
Present	405 (13·6)	272 (13·9)	108 (13·6)	25 (11·2)		185 (15.2)	
TRAb IU/L	7·8 (3·2, 18·4)	6·4 (2·9, 14·0)	11·4 (4·2, 27·0)	16·4 (5·6, 37·5)	<0·001	5.8 (2.75, 12.9)	<0.001
Thyroid status							
FT4, pmol/L	31·8 ± 22·0	29·5 ± 19·7	36·2 ± 25·4	36·5 ± 25·6	<0·001	—	
FT4 >40 pmol/L	719 (24)	390 (20)	255 (32)	74 (33)	<0·001	—	
Missing tests	1220 (29)	1144 (37)	33 (4)	43 (16)	<0.001	—	

Supplementary Table 3: Baseline characteristics in patients with missing and non-missing thyroid function tests

Data represents numbers (%), mean ± SD, or median (interquartile range). TRAb, TSH receptor antibody; a, P values are for trend across treatment categories in patients with thyroid tests. b, P values are for difference between missing and non-missing tests.

	ATD	RAI-Group-A	RAI-Group-B	P value
Number (%)	3587 (89%)	250 (6%)	182 (5%)	
Age				
Mean ± SD	46·9 ± 15·8	52·6 ± 15·0	52·9 ± 15·8	<0·001[a, b]
Range	18-92	19-88	20-92	
Gender				
Male	642 (17·9%)	55 (22·0%)	41 (22·5%)	0·089
Female	2945 (82·1%)	195 (78·0%)	141 (77·5%)	
Comorbidity				
Present	485 (13·5%)	35 (14·0%)	30 (16·5%)	0·728
Absent	3102 (86·5%)	215 (86·0%)	152 (83·5%)	
TRAbs, U/L	6·7 (3, 15·8)	11·2 (4·1, 26·6)	11·4 (4·4, 26·1)	<0·001[a, b]
Radioiodine therapy				
Dose, Mbq	-	555 (546, 563)	555 (544, 566)	0·984[d]
Days from diagnosis to treatment	-	108 (53, 178)	188 (88, 302)	<0·001 [d]
FT4, pmol/L				
Baseline	31·2 ± 21·8	35·2 ± 25·2	34·8 ± 21·7	<0·003[a, b]
12 months	17·4 ± 9·3	15·9 ± 7·3	21·5 ± 10·6	<0·001[a, b, c]
Baseline – 12 months	16·1 ± 23·0	21·1 ± 26·9	13·9 ± 21·3	<0·001[b, c]
TSH at 12 months, mU/L				
Low	770 (39·6%)	44 (18·9%)	84 (64·6%)	<0·001 [a, c]
Normal	905 (46·5%)	41 (17·7%)	36 (27·7%)	
High	272 (13·9%)	147 (63·4%)	10 (7·7%)	

Supplementary Table 4: Characteristics of patients in the one-year landmark cohort

a ATD vs RAI-Group-A, b ATD vs RAI-Group-B, c RAI-Group-A vs RAI-Group-B; ANOVA with pairwise comparisons with Tukey's test; d RAI-Group-A vs RAI-Group-B, Kruskal Wallis; data is in numbers (%), mean + standard deviation, or median (interquartile range). Excluded patients who had surgery in the first 12 months (n=78) or <12 months survival (n=89).

	All-Cause Mortality			MACE		
	Events/Total, N	**HR (95% CI)**	**P value**	**Events/Total, N**	**HR (95% CI)**	**P value**
Whole cohort						
ATD	145/3527	1·00 (Ref)		176/3384	1·00 (Ref)	
RAI-Group-A	13/236	0·47 (0·27, 0·83)	0·009	17/224	0·49 (0·30, 0·81)	0·005
RAI-Group-B	21/174	1·52 (0·96, 2·42)	0·083	21/159	1·49 (0·94, 2·35)	0·089
No comorbidities						
ATD	82/3047	1·00 (Ref)		118/2982	1·00 (Ref)	
RAI-Group-A	4/201	0·20 (0·07, 0·56)	0·002	7/195	0·25 (0·12, 0·54)	0·001
RAI-Group-B	13/146	1·45 (0·80, 2·63)	0·195	16/137	1·68 (0·99, 2·84)	0·052
Age≥50 yrs						
ATD	129/1502	1·00 (Ref)		152/1387	1·00 (Ref)	
RAI-Group-A	11/137	0·43 (0·23, 0·79)	0·007	15/127	0·46 (0·27, 0·79)	0·005
RAI-Group-B	19/96	1·52 (0·93, 2·48)	0·102	17/84	1·36 (0·82, 2·25)	0·236
Age<50 yrs						
ATD	16/2025	1·00 (Ref)		24/1997	1·00 (Ref)	
RAI-Group-A	2/99	1·04 (0·23, 4·79)	0·963	2/97	0·74 (1·70, 3·18)	0·680
RAI-Group-B	2/78	1·36 (0·31, 6·09)	0·691	4/75	2·32 (0·79, 6·78)	0·125

Supplementary Table 5: Mortality and MACE by primary treatment: excluding pregnant patients

HR (95% CI) are obtained from multivariable Cox proportional hazard regression models. Analysis was conducted in all patients and in subgroups according to treatment in the first-year. ATD, Antithyroid drugs, RAI-Group-A, radioiodine treatment with control of hyperthyroidism, RAI-Group-B, radioiodine treatment without control of hyperthyroidism

	All-Cause Mortality			MACE		
	Events/Total, N	**HR (95% CI)**	**P value**	**Events/Total, N**	**HR (95% CI)**	**P value**
Whole cohort						
ATD	142/3353	1·00 (Ref)		166/3215	1·00 (Ref)	
RAI-Group-A	13/229	0·46 (0·26, 0·82)	0·009	17/218	0·50 (0·30, 0·83)	0·007
RAI-Group-B	21/166	1·53 (0·96, 2·44)	0·071	19/151	1·38 (0·86, 2·33)	0·184
No comorbidities						
ATD	82/2903	1·00 (Ref)		114/2841	1·00 (Ref)	
RAI-Group-A	4/197	0·20 (0·07, 0·54)	0·002	7/192	0·25 (0·12, 0·54)	0·001
RAI-Group-B	13/139	1·44 (0·79, 2·60)	0·119	15/130	1·62 (0·94, 2·77)	0·082
Age≥50 yrs						
ATD	126/1408	1·00 (Ref)		142/1297	1·00 (Ref)	
RAI-Group-A	11/131	0·42 (0·22, 0·78)	0·006	15/121	0·48 (0·28, 0·82)	0·007
RAI-Group-B	19/89	1·53 (0·94, 2·50)	0·089	15/77	1·23 (0·72, 2·11)	0·443
Age<50 yrs						
ATD	16/1945	1·00 (Ref)		24/1918	1·00 (Ref)	
RAI-Group-A	2/98	1·02 (0·22, 4·69)	0·984	2/97	0·72 (1·67, 3·11)	0·660
RAI-Group-B	2/77	1·38 (0·31, 6·16)	0·673	4/74	2·31 (0·79, 6·74)	0·126

Supplementary Table 6: Mortality and MACE by primary treatment: excluding patients with borderline TRAbs

Patients with borderline TRAbs (1.0-1.5 IU/L) were excluded. HR (95% CI) are obtained from multivariable Cox proportional hazard regression models. Analysis was conducted in all patients and in subgroups according to treatment in the first-year. ATD, Antithyroid drugs, RAI-Group-A, radioiodine treatment with control of hyperthyroidism, RAI-Group-B, radioiodine treatment without control of hyperthyroidism

	Model 1		Model 2	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age, years [a]	1·09 (1·08, 1·10)	<0·001	1·09 (1·08, 1·10)	<0·001
Sex				
Male	1·00	Ref	1·00	Ref
Female	0·57 (0·43, 0·76)	<0·001	0·65 (0·47, 0·90)	0·010
Co-morbidity				
Absent	1·00	Ref	1·00	Ref
Present	3·07 (2·29, 4·13)	<0·001	3·30 (2·36, 4·63)	<0·001
Year of diagnosis [b]	0·68 (0·58, 0·79)	<0·001	0·63 (0·54, 0·79)	<0·001
Baseline TRAb [c]	1·15 (0·99, 1·32)	0·069	1·14 (0·96, 1·35)	0·144
Thyroid hormones				
Baseline FT4 [d]	—	—	0·99 (0·99, 1·00)	0·474
Baseline TSH	—	—		
TSH 0.1—0·4 mU/L			1·00	Ref
TSH <0·1 mU/L			0·99 (0·95, 1·02)	0·384
Serial FT4 [d]	—	—	1·40 (1·11, 1·77)	0·005
Serial TSH				
Normal/High	—	—	1·00	Ref
Low	—	—	1·00 (0·66, 1·54)	0.980
Treatment				
ATD	1·00	Ref	1·00	Ref
RAI without hyperthyroidism control	0·91 (0·67, 1·25)	0·571	0·97 (0·70, 1·36)	0·863
RAI with hyperthyroidism control	0·26 (0·08, 0·82)	0·022	0·27 (0·09, 0·87)	0·028
Thyroidectomy	0·60 (0·15, 2·44)	0·472	0·33 (0·05, 2·39)	0·272

Supplementary Table 7: Multivariable analysis for all-Cause mortality

HR (95% CI) are obtained from multivariable Cox proportional hazard regression models. Model 1, all patients, n=4189; Model 2, patients with thyroid function tests, n=2969; Serial thyroid hormones and treatment were set as time-dependent covariates. Patients contributed person-years of treatment from diagnosis to radioiodine treatment or thyroidectomy (ATD), following radioiodine to control of hyperthyroidism (RAI without hyperthyroidism control), following radioiodine and control of hyperthyroidism (RAI with hyperthyroidism control), and following thyroidectomy (thyroidectomy). a, HR per 5-year increase in age; b, HR per 5-year increase in diagnosis year, c, HR per 10 IU/L increase in TRAb concentration, d, HR per 10 pmol/L increase in FT4 concentration

	Model 1		Model 2	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age, years	1·08 (1·07, 1·09) [a]	<0·001	1·08 (1·07, 1·09) [a]	<0·001
Sex				
Male	1·00	Ref	1·00	Ref
Female	0·56 (0·44, 0·71)	<0·001	0·61 (1·07, 1·09)	<0·001
Co-morbidity				
Absent	1·00	Ref	1·00	Ref
Present	2·91 (2·28, 3·72)	<0·001	2·95 (2·22, 3·91)	<0·001
Year of diagnosis	0·75 (0·67, 0·85) [b]	<0·001	0·74 (0·64, 0·86) [b]	<0·001
Baseline TRAb	1·04 (0·93, 1·17) [c]	0·493	1·06 (0·92, 1·22) [c]	0·404
Thyroid hormones				
Baseline FT4	—	—	0·99 (0·99, 1·00) [d]	0·618
Baseline TSH	—	—		
TSH 0.1—0·4 mU/L			1·00	Ref
TSH <0·1 mU/L			0·99 (0·96, 1·01)	0·317
Serial FT4	—	—	1·52 (1·09, 1·94) [d]	0·007
Serial TSH				
Normal/High	—	—	1·00	Ref
Low	—	—	1·00 (0·89, 1·78)	0.990
Treatment				
ATD	1·00	Ref	1·00	Ref
RAI without hyperthyroidism control	1·02 (0·78, 1·34)	0·857	1·08 (·081, 1·43)	0·601
RAI with hyperthyroidism control	0·44 (0·20, 0·94)	0·033	0·45 (0·21, 0·96)	0·040
Thyroidectomy	0·35 (0·09, 1·43)	0·144	0·19 (0·03, 1·40)	0·103

Supplementary Table 8: Multivariable analysis for MACE

HR (95% CI) are obtained from multivariable Cox proportional hazard regression models. Model 1, all patients, n=4189; Model 2, patients with thyroid function tests, n=2969; Serial thyroid hormones and treatment were set as time-dependent covariates. Patients contributed person-years of treatment from diagnosis to radioiodine treatment or thyroidectomy (ATD), following radioiodine to control of hyperthyroidism (RAI without hyperthyroidism control), following radioiodine and control of hyperthyroidism (RAI with hyperthyroidism control), and following thyroidectomy (thyroidectomy). a, HR per 5-year increase in age; b, HR per 5-year increase in diagnosis year, c, HR per 10 IU/L increase in TRAb concentration, d, HR per 10 pmol/L increase in FT4 concentration